# Central Nervous System Disease in Langerhans Cell Histiocytosis

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Langerhans cell histiocytosis (LCH) is a rare disease of the monocyte-macrophage system. The clinical presentation ranges from a single bone lesion to widespread multiorgan involvement. The course is unpredictable, with a spectrum of spontaneous regression, chronic recurrences for years, or a rapidly fatal deterioration.[1,2] Because of the frequent involvement of the cranial bones and the hypothalamic-pituitary region (HPR) with diabetes insipidus (DI) as key manifestation, LCH has long been recognized to be closely related to the central nervous system (CNS).[3] In the past decade, a wide variety of other CNS findings have been described with magnetic resonance imaging (MRI) scans, with or without associated clinical neuroendocrine findings.[4-6]

The rarity of CNS LCH and the varied clinical presentation has impeded research in this field. The quality of the diagnostic examination and follow-up of patients who are scattered over the globe has been variable, leading to difficulties in comparing treatments and outcomes. Although the therapy of multisystem LCH has been subject to multicenter international clinical trials in the past 20 years, treatment experience in CNS disease is limited to anecdotal cases and small pilot studies. However, despite the problems associated with studying a rare disease with an unknown course and varied natural history, research in CNS LCH has made considerable progress in the past 2 decades because of the efforts of the LCH CNS study group of the Histiocyte Society (HS) and some single and multi-institutional collaborative efforts.

In this review, we provide a comprehensive description of the spectrum and course of MRI changes, the underlying neuropathology, the clinical pattern and course, and the risk factors for CNS LCH and the available therapeutic experience. This information stems from: (1) the database of the LCH Study Reference Center of the HS that comprises data on 308 patients with LCH with (intra)cranial lesions studied with MRI, including 153 patients with LCH-associated neurodegeneration registered in the HS LCH CNS study[7] and (2) a review of the relevant literature.

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| ARA-C | Cytosine arabinoside |
| CSF | Cerebrospinal fluid |
| CNS | Central nervous system |
| DI | Diabetes insipidus |
| FDG | Fluorodeoxyglucose |
| HPR | Hypothalamic pituitary region |
| HS | Histiocyte Society |
| IGIV | Imunoglobulin intravenously |
| LCH | Langerhans cell histiocytosis |
| MRI | Magnetic resonance imaging |
| PET | Positron emission tomography |
| T1WI | T1-weighted images |
| T2WI | T2-weighted images |
| VRS | Virchow-Robin spaces |

## Imaging Features

### Magnetic Resonance Imaging Findings and Differential Diagnoses

In the past 15 years, the knowledge and understanding of the brain MRI findings in patients with LCH has grown. In the LCH CNS Study Reference Center, a review of 935 MRI investigations in 308 patients with LCH was undertaken (D.P.) and resulted in the classification presented in the Table.

### Intracranial Tumorous Lesions (Figure 1)

The radiographic findings associated with DI have been described in detail in the past 2 decades. In the HPR, the characteristic features consist of enlargement of the pituitary stalk with potential progression to space-occupying tumors extending to the pituitary and hypothalamus. In DI, there is typically a "loss of bright spot" (ie, the lack of the physiologic hyperintense signal of the posterior pituitary on T1-weighted images [T1WI]), which correlates with the loss of antidiuretic hormone-containing granules.[8]

The LCH-associated pineal gland abnormalities comprise solid masses or cystic lesions. Grois et al found pineal gland lesions including cystic changes and enlargement in 63% of patients with LCH studied with MRI and an interesting association between pineal gland enlargement and enlargement of the pituitary stalk.[3] The co-existing changes in these 2 regions might be caused by their functional interactions, because both structures belong to the circumventricular organs that are located outside the blood brain barrier and changes also are observed in other diseases.[9]

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Supported by the Histiocytosis Association of America and by Shelta Australia. The authors declare no conflicts of interest.

0022-3476/$ - see front matter.  10.1016/j.jpeds.2010.03.001

**Table. Classification of magnetic resonance imaging changes on the basis of the findings in 308 patients with Langerhans cell histiocytosis patients and intracranial lesions studied with 935 magnetic resonance imaging investigations**

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|---|
| **Tumorous/Granulomatous lesions** |
| Granulomatous lesions of skull bones |
| Hypothalamic pituitary region |
| Posterior pituitary |
| Anterior pituitary |
| Pituitary stalk |
| Hypothalamus |
| Pineal gland |
| Choroid plexus |
| Meninges |
| Enhancing parenchmal lesions |
| **Non-tumorous/Non-granulomatous intracerebral lesions** |
| Dentate nucleus* |
| Cerebellar white matter* |
| Basal ganglia* |
| Brainstem, pons* |
| Supratentorial white matter |
| Virchow Robin spaces |
| **Atrophy** |
| Cerebellar atrophy |
| Midbrain atrophy |
| Supratentorial atrophy |

*Radiologic neurodegeneration

Other space occupying tumorous lesions occur rarely in the meninges, choroid plexus, and in the brain parenchyma. They can occur as single or multiple lesions with a signal intensity corresponding to soft tissue. Choroid plexus lesions are characterized by marked signal loss on T2-weighted images (T2WI) suggesting calcification.[10,11]

Parenchymal granulomatous lesions can show a random or vascular distribution pattern. The differential diagnosis includes craniopharyngioma, germ-cell tumor, sarcoidosis, other histiocytic diseases such as Erdheim Chester or Rosai Dorfman disease, and other rare entities.[11]

### Intracranial Non-Tumorous Lesions (Figure 2)

The second most frequent presentation of CNS LCH, excluding HPR disease, is a combination of pathologic changes in the cerebellum, basal ganglia, and/or pons with characteristic MRI patterns. Findings include symmetric, hyperintense signal changes on T2WI and hypo- or hyper-intense signals on T1WI in the cerebellar grey matter alone, extending to the surrounding white matter, or presenting as cerebellar atrophy, sometimes combined with T2-weighted hyperintense changes of the pons. In the basal ganglia, the abnormalities consist of hyperintense signals on T1WI and variable signal intensities on T2WI, usually involving the globus pallidum. Less frequently, the brain stem and forebrain are involved.[10-13] Prosch et al termed this pattern "radiological neurodegeneration."[14]

Apart from the extension of these so-called "neurodegenerative" lesions, there are 2 other types of parenchymal white matter changes: (1) the frequently found dilated Virchow-Robin spaces (VRS) and (2) the rare leukoencephalopathy-like pattern.

Dilated VRS are best seen on T2WI and can be barely visible with a width of approximately 2 mm. The role of VRS in the pathophysiology of CNS-LCH remains to be investigated. No biopsy samples to confirm histopathology were available from such lesions, but they might be consistent with either an active inflammatory process or the sequelae of an inflammatory process. Caution should be observed when evaluating VRS on MRI scans performed on modern 3 Tesla machines, because VRS are visible on high-field MRI in almost all patients.

The leukoencephalopathy-like pattern involves the cerebellar white matter, the pons, and the periventricular white matter and presents with symmetric patchy areas characterized by high signal intensity on T2WI and low signal intensity on T1WI without a clear vascular distribution.[11] The differential diagnosis of this pattern includes acute disseminated encephalomyelitis, acute multiphasic disseminated encephalitis, disseminated encephalitis, and diverse metabolic or degenerative disorders including leukencephalopathy caused by chemotherapy or radiation.[11] Atrophy is not a common finding and may be localized to the cerebellar hemispheres. However, atrophy can also be global, usually in patients with a progressive symptomatic course (Figure 3).[11,13]

## Experimental Imaging Studies

Positron emission tomography (PET) studies with the tracer fluorodeoxyglucose (FDG-PET) were reported in a few cases as showing an increased tracer uptake in tumorous lesions and lesions enhancing on MRI[15] and a decreased uptake in the cerebellum corresponding to lesions of a neurodegenerative pattern.[16,17-19] Single photon emission computed tomography with [$^{123}$I] 2-beta-carbomethoxy-3-beta-(4-iodophenyl)tropane and [$^{123}$I]iodobenzamide, a method assessing the function of the nigrostriatal system, did not reveal any abnormality in a case with only neurodegeneration.

Proton magnetic resonance spectroscopy measures the concentration of neuronal metabolites. A decreased peak of N-acetyl-aspartate infratentorially was found in the same patient, reflecting neuronal damage and loss in the cerebellum in keeping with the neuropathologic findings.[16] The value of all these methods needs further exploration.

## Neuropathology

In 1979, Kepes provided a detailed treatise on the pathology of CNS lesions in LCH, on the basis of conventional examination of autopsy material and described lesions extending to the CNS from neighboring bones, meningeal involvement, and diffuse or circumscribed intraparenchymal lesions.[20] More than 2 decades later, the LCH CNS co-operative group reviewed brain samples of 12 patients with CNS LCH, applying modern immunocytochemical techniques, and correlated the findings to MRI changes and clinical findings.[21] There are 3 types of lesional patterns in CNS LCH. In the first, circumscribed granulomas within the brain's connective tissue spaces demonstrate a composition similar to LCH

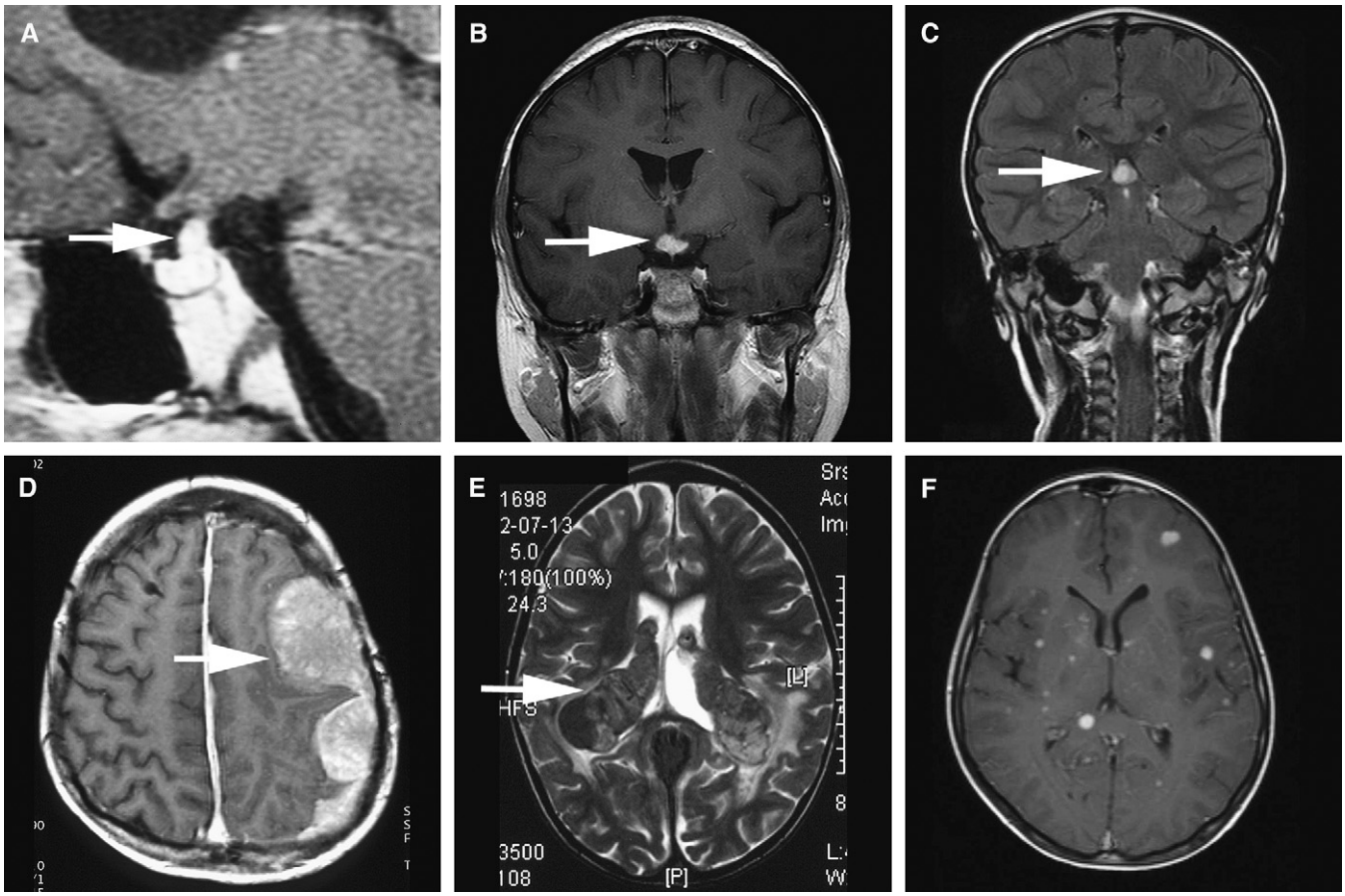


**Figure 1.** Tumorous LCH lesions. **A,** Sagittal contrast enhanced T1-weighted image demonstrating a significantly thickened pituitary stalk (*arrow*). **B,** Coronal contrast enhanced T1-weighted image showing a hypothalamic mass lesion **C,** Coronal contrast enhanced T1-weighted image showing an enhancing lesion in the pituitary gland (*arrow*). **D,** Contrast enhanced T1-weighted image showing extensive meningeal lesions (*arrow*). **E,** Axial T2-weighted image showing bilateral hypointense (calcified) lesions in the choroid plexus (*arrow*). **F,** Axial contrast enhanced image showing multiple sharply demarcated enhancing lesions in random distribution.

granulomas in peripheral organs, including a variable presence of CD1a+ cells, but accompanied by pronounced CD8+ T-lymphocytic infiltration. These granulomas have a predilection to involve the circumventricular organs, such as the pituitary stalk, that lack a blood-brain barrier. In the second, neurodegenerative lesions mainly affect the cerebellum and the brain stem. In these lesions, CD1a+ cells are missing, but there is a profound inflammatory process, dominated by CD8+ lymphocytes that are associated with neuronal and axonal degeneration and secondary myelin loss. The massive neuronal and axonal loss in the cerebellum results in atrophy of the cerebellar cortex and white matter. In the third pattern, granulomas in infundibular tumors invade the hypothalamus and show diffuse infiltration of the surrounding CNS parenchyma by CD1a+ histiocytes and are surrounded by neurodegeneration (ie, a pronounced loss of axons and neurons in the adjacent parenchyma with intense CD8+ T-lymphocyte-dominated inflammation).[21]

On the basis of these findings, it is intriguing to speculate on the pathogenesis of neurodegenerative disease in LCH. From long-standing chronic, recurrent, or extensive granulomatous lesions in the craniofacial bones, the pathologic process may propagate to the intracranial space. Intracranial granulomas (eg, in the HPR or meninges) may then stimulate chemokine/cytokine mediated tissue damage in the vicinity of granulomas or initiate an autoimmune response to brain tissue components induced by antigen presentation through microglial cells or Langerhans cells that may persist and continue even after the resolution of the LCH granuloma itself.

## Clinical Features

Clinical symptoms depend on the site and the type of CNS involvement. DI, the hallmark of infiltration in the hypothalamic pituitary region, is seen in as many as 25% of all patients with LCH or in as many as 50% of patients with multisystem disease.[22-26] Growth hormone deficiency is the

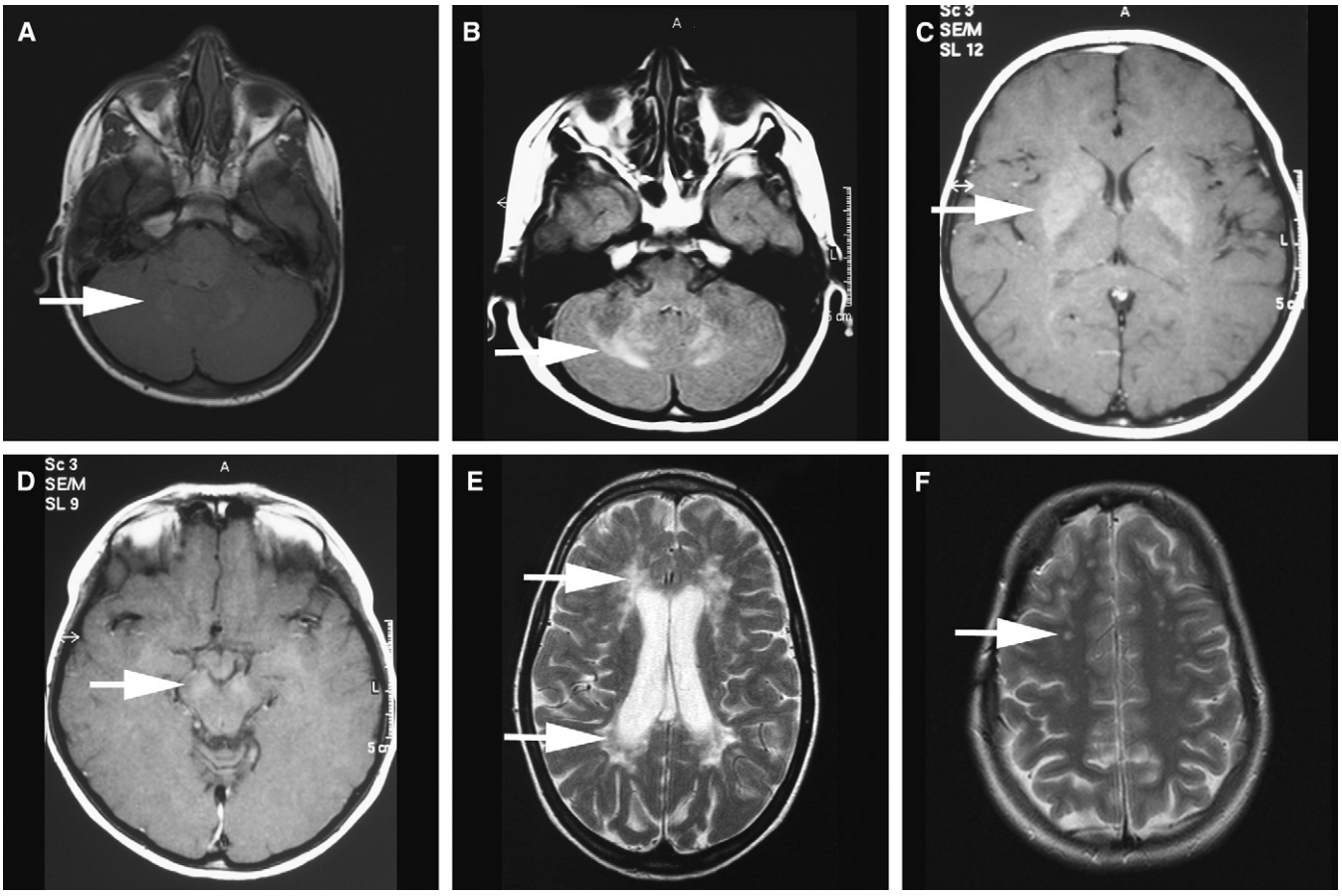


**Figure 2.** Non-granulomatous LCH lesions. **A,** Axial T1-weighted image showing subtle hyperintense signal alterations in the dentate nucleus (*arrow*) corresponding to radiological neurodegenerative LCH. **B,** Fluid attenuated inversion recovery (FLAIR) sequence showing extensive hyperintense signal alterations in the cerebellar white matter (*arrow*) corresponding to more pronounced radiological neurodegenerative LCH. **C,** Axial T1-weighted image showing hyperintense signal alterations in the basal ganglia (*arrows*). Also, these signal alterations are considered to be radiological neurodegenerative LCH. **D,** Axial T1-weighted image showing hyperintense signal alterations cerebral peduncles (*arrows*). **E,** Axial T2-weighted images showing patchy hyperintense signal alterations around the anterior and posterior horn of the lateral ventricles corresponding to a leukoencephalopathy like pattern (*arrows*). **F,** Axial T2-weighted image showing accentuated Virchow Robin spaces (*arrow*).

second most frequent endocrinopathy observed in patients with LCH and affects approximately 10% of patients with LCH.[27,28] Overall, anterior pituitary hormone loss, such as growth hormone deficiency, secondary hypothyroidism, hypogonadism, and hyperprolactinemia, develop in as many as 60% of patients with DI.[23,25]

In the absence of a history of LCH, isolated central DI presents a diagnostic challenge. A variety of other diseases, in particular germinoma, must be excluded.[29,30] A thorough and 3- and 6-month repeated diagnostic evaluation schedule is mandatory to search for extracranial LCH lesions. An algorithm for the diagnostic evaluation of patients with central DI including MRI, full clinical evaluation, and cerebrospinal fluid (CSF) studies was proposed by Prosch et al.[31] Biopsy of the HPR is only recommended in tumors >6 mm maximal diameter and in the absence of extracranial lesions.[29,30]

Tumorous lesions in the meninges or choroid plexus are rare and can lead to headaches, seizures, and other focal symptoms and obstruction of the ventricles with increased intracranial pressure and hydrocephalus.[3,11]

LCH-associated neurodegenerative lesions are associated with a highly variable clinical picture. Many patients are free of neurologic symptoms despite typical MRI changes of "radiologic neurodegeneration" for years. Other patients, however, can have "clinical neurodegeneration," with a spectrum of clinical signs ranging from subtle tremor or mild abnormalities of the reflexes, discrete gait disturbance, dysarthria, dysphagia, and motor spasticity to pronounced ataxia, behavioral disturbances, learning difficulties, or even severe psychiatric disease.[4,6]

The first long-term follow-up observations in a small group of patients with radiologic neurodegeneration indicated that ND LCH seems to be progressive with MRI in most patients[14,32] and leads to clinical neurocognitive symptoms in approximately 25% of cases at a median of 6 years after initial diagnosis of LCH. However, longitudinal studies

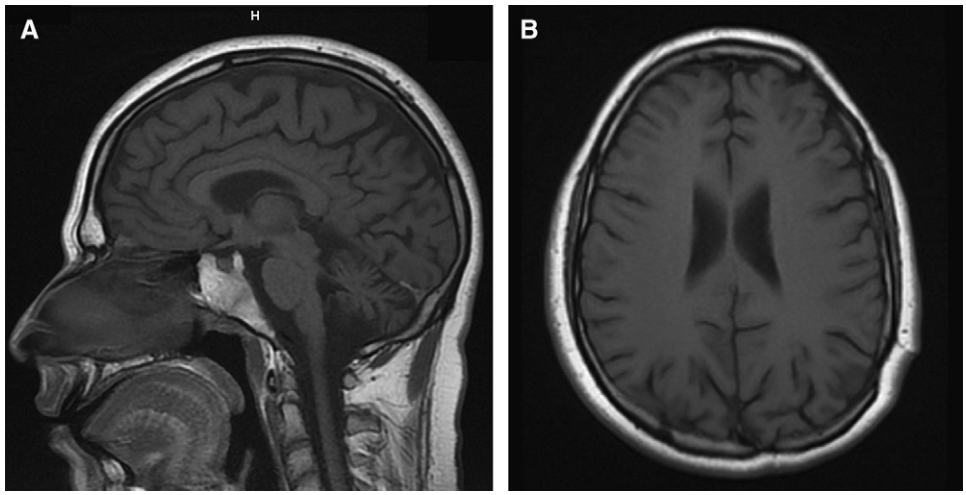


**Figure 3.** Atrophy. **A,** Axial T1-weighted image showing dilated cerebral sulci not appropriate to the age of the patient (18 years). **B**, Sagittal T1-weighted image from the same patient showing significant cerebellar atrophy.

of ND LCH in a greater number of patients are necessary to better define the natural history.

Several studies have described global cognitive deficits and changes in memory and concentration/attention and perceptual-organizational changes in patients with LCH.[33-38]

Thus far, CSF studies have not been performed consistently or in a standardized fashion and have only been reported in a minority of patients. No typical pattern can be recognized from the few samples analyzed.[39]

## Risk Factors for Central Nervous System Langerhans Cell Histiocytosis

Approximately 50% of cranial MRIs of patients with LCH exhibit lesions in the craniofacial bones.[40] Lytic lesions of the calvaria are very common and may erode the dura, but usually do not penetrate deeply enough to injure the underlying cortex. Lesions of the base of the skull or facial bones, including temporal, sphenoidal, ethmoidal, zygomatic, ethmoidal, and orbital bones, may be associated with considerable soft tissue extension with extradural involvement. The paranasal sinuses or mastoids are opacified in >50% of patients with LCH examined with MRI, corresponding to fluid or to polyps and soft tissue with contrast enhancement. Such sinus and mastoid changes were significantly more frequent in patients with LCH than in control patients with brain tumors, epilepsy, metabolic diseases, and other diseases.[11] Biopsy results of sinus or mastoid regions were only available in a few cases, revealing active LCH and nonspecific inflammatory tissue. Biopsy of sinuses, mastoids, or both that show abnormalities on imaging studies should be considered in cases of otherwise isolated hypothalamic pituitary disease or isolated radiologic neurodegeneration, to avoid a CNS biopsy.[31] Patients with craniofacial lesions involving the orbital, temporal, sphenoid, ethmoid, or mastoid bones and the paranasal sinuses and anterior or middle cranial fossa seem to have a higher risk of the development of DI and other CNS manifestations.[21,23,41,42] There has been debate whether such lesions should be regarded as "CNS risk lesions"[43] and be treated systemically.[44,45] To assess the impact of such lesions on the risk of the development of DI or radiologic neurodegeneration, standardized long-term follow-up studies, including MRI examinations, are needed. There is evidence that chronic or reactivating disease was associated with increased endocrine and CNS problems.[24,25] Long-standing disease activity is a risk factor that increases the risk for DI and further CNS complications. It was shown that longer maintenance therapy leads to a lower rate of reactivations.[46] Further prospective studies are needed to test whether prolonged therapy reduces CNS disease.

In addition to the well-recognized risk of progressive loss of anterior pituitary hormones, patients with DI seem to have an increased risk of the development of signs of radiologic neurodegeneration.[23-25,47] Grois et al found a high frequency (76%) of signs of radiologic neurodegeneration on MRIs of patients with DI observed for >5 years. Donadieu et al described LCH-associated neurodegeneration in approximately 10% patients with pituitary involvement (14/145) compared with 0.2% (1/444) in patients without pituitary involvement.[25] Wnorowski et al found that the incidence of radiologic neurodegeneration ranged between 4% (of the overall LCH study population of 1215 patients) and 57% (of the 83 selected patients who had ≥2 MRI investigations). All 47 patients with signs of radiologic neurodegeneration, clinical neurodegeneration, or both had lesions involving the craniofacial bones or intracranial tumorous lesions before the diagnosis of neurodegeneration with MRI.[32] Only patients with LCH and specific clinical indications who might carry a potential risk for CNS disease usually undergo brain MRI examinations (ie, patients with craniofacial lesions, an endocrinopathy, or abnormal

neurologic findings). Therefore, the true frequency of radiologic neurodegeneration cannot be determined. In a single center study, Mittheisz et al found evidence that 20% of patients with LCH had radiologic neurodegeneration.[33] Similarly, in a population-based study from Sweden, Laurencikas et al found a minimum prevalence of 24% radiologic neurodegeneration.[48]

## Therapeutic Experience and Recommendations

Information on the treatment of CNS LCH is limited. Only a few series with small numbers of patients or case reports have been published. The quality of the treatment data on the patients registered in the CNS study was very heterogeneous. Patients with different types of CNS disease were treated at different disease stages for different intervals. Variable evaluation at diagnosis and during the follow-up impeded a critical evaluation and comparison of the efficacy of the various treatment approaches. Accordingly, judgment of the efficacy of treatment is problematic.

Therapy recommendations by the experts of the CNS LCH study group are based on published data, but also reflect their cumulative experience with treating and consulting on these challenging cases.

### Tumorous Lesions

The management of new onset DI has been controversial. DI can occur as a presenting symptom of LCH with or without lesions in other organs, or it can develop upon reactivation years after the initial presentation. According to our current understanding, new onset DI is a sign of active LCH infiltration in the hypothalamic pituitary region, even when the degree of infiltration does not manifest as a tumorous lesion in the pituitary stalk with MRI. The therapeutic goal in HPR disease is to prevent tissue damage by the infiltrate, hormone loss, and possibly the development of cerebellar neurodegeneration as a long-term consequence that may lead to significant neurological impairment.

In the various reports, the diagnosis of DI was based on different criteria, which prevents the comparison of the different studies. In some cases, no information on the size of mass lesions before and after therapy was given. DI was sometimes only diagnosed clinically with the presence of polyuria and polydipsia, but not proven with water deprivation testing. The reported treatment regimens have included standard LCH chemotherapies (prednisone, vinblastine, etoposide) or alternative drugs like 2-chloro-deoxyadenosine (cladribine).[49] Irradiation also was used in a few cases.[27,50-52] However, because of its potential adverse late effects, radiation therapy is not recommended as a treatment of choice. Assessment of response also was arbitrary; in some reports, "response" referred to a "radiologic response" with regression of a mass lesion in the HPR. "Clinical response" was defined as resolution of DI or decreased need for hormone substitution therapy. In 61 of 144 published cases, no information on radiologic responses was reported. In 20 of the remaining 83 patients, a radiologic response on MRI was documented. Clinical response with a complete resolution of DI has been reported in 9 patients.[27,49-51,53-55] On the basis of these data, no single treatment or regimen proved to be superior.

A few case reports have been published on focal tumorous lesions arising from intracranial regions other than the hypothalamic pituitary axis (eg, meningeal tumors, characteristic neurodegenerative LCH changes, or both). Treatment modalities, including surgery,[56] radiation,[10] standard LCH therapy,[10] and 2-CDA[55,57,58] or imatinib mesylate, a tyrosine kinase inhibitor,[59] have shown radiologic responses in some patients with tumorous lesions and in some instances patients with neurodegenerative changes, although the clinical signs and symptoms have not been shown to be reversible.

On the basis of the available information, the CNS study group recommends the initiation of systemic chemotherapy (depending on earlier treatments), promptly after the new onset of DI (even in case of normal findings with the HPR or only subtle thickening of the pituitary stalk) or the diagnosis of a tumorous intracranial lesion to prevent further damage. Tumorous lesions in the HPR, the meninges, or choroid plexus are located outside the blood-brain barrier and, therefore, may be accessible for systemic therapy. Long-term studies on the prevention of further hormone deficiencies and neurodegeneration are planned in the frame of the forthcoming LCH IV study of the HS.

### Langerhans Cell Histiocytosis-Associated Neurodegenerative Lesions

The situation for LCH-associated neurodegenerative lesions that may or may not be associated with clinical symptoms is even more complex. The optimal timing and type of treatment is unclear. The various therapeutic approaches reflect the different pathogenic hypotheses and comprise chemotherapy, anti-inflammatory medications, and anti-angiogenic medications. Immunomodulatory and neuroprotective agents have also been used on occasion.

Thus far, only series involving small numbers of patients report on the effectiveness of different treatment strategies on the development and the course of neurodegeneration. The assessment and monitoring of patients has been variable as well. In a French study by Idbaih et al,[60] retinoic acid was administered to 10 patients with radiologic and clinical neurodegeneration. All 10 patients remained clinically stable, but the observation time was only 1 year and might be too short to judge the response adequately. Dhall et al[49] studied 12 patients with tumors in the hypothalamic pituitary region and neurodegeneration who were treated with cladiribine, but no reversal of clinical signs and symptoms was observed. Imashuku et al[61] treated 4 patients with clinical neurodegeneration with a regimen containing immunoglobulin intravenously (IGIV) for >12 months and found what was considered a delay in neurologic deterioration in treated patients compared with 8 patients who did not receive IGIV. In 2008, Henter's group reported on a 12-year experience of IGIV in a patient severely affected by ND-LCH, for whom treatment appeared beneficial in halting progression of ND-LCH.[39] McClain's group[62] has treated

8 patients with vincristine/cytosine arabinoside (ARA-C) or ARA-C alone; 5 of 8 patients had improvement in clinical signs and brain MRI results. Follow-up of these patients ranged from 2 months to 7 years.

In the LCH CNS registry, the recent most frequently used, second-line treatment strategies were cladiribine or ARA-C. Eighteen patients with intracranial disease from the LCH registry were treated with cladiribine. There was radiologic response in tumorous lesions in 70% of patients with MRI. Fourteen of the 18 patients were reported to have radiologic neurodegeneration. Six patients were treated with ARA-C for various (intra)cranial lesions. Tumorous lesions regressed on MRI. Signs of radiologic neurodegeneration, however, remained stable in 2 patients during a median of 3 months and worsened in another 2 patients in a median period of 7 months. In the remaining 2 patients, therapy response was not assessable because of a lack of MRI (LCH CNS Study, unpublished).

There is controversy whether patients with radiologic signs of neurodegeneration, but without clinical symptoms, should be treated. However, studies in other neurodegenerative diseases such as multiple sclerosis, Alzheimer disease, or amyotrophic lateral sclerosis,[63-65] showed that approximately 50% to 80% of neurons must be lost before the brain's capacity for compensation is exceeded and neurologic disabilities become overt. Considering these findings, one may speculate that early therapeutic intervention in cases of radiologic neurodegeneration in the absence of clinical symptoms possibly could arrest the pathologic process and prevent loss of additional neurons that eventually leads to irreversible symptoms. Unfortunately, definitive evidence for changing the course of patients with clinical symptoms has not been obtained, making such a recommendation premature, and we support the need for a formal study with a standardized diagnostic and follow-up evaluation.

## Recommendations

After almost 20 years of research on CNS LCH, there are still considerable gaps in understanding the disease process and its course. It is still controversial whether CNS disease with its neuroendocrine problems might be influenced by any therapy. Some authorities believe that neurodegeneration, in particular, is an immune process independent from LCH activity, and others believe that early and effective LCH therapy may prevent or at least ameliorate the development of CNS complications.

In an attempt to make further progress in this field, the HS currently is developing a new protocol for LCH (LCH-IV), due to be launched in 2010, which will include guidelines for the diagnostic work-up and recommendations for treatment of CNS LCH. In general, these guidelines will recommend repeated MRIs, standardized neurologic evaluation, and neuopsychological tests for all patients with CNS disease. The study will test whether prolonged continuation of therapy will reduce the rate of reactivation and thereby the rate of CNS disease. Although the choice of treatment for neurodegenerative disease will be left to the discretion of the treating physician, we strongly recommend joining this international effort to improve our understanding of this devastating disorder. ■

*The authors are grateful to Oussama Abla, Maurizio Arico, Itziar Astigarraga, Karin Beutel, Helmut Gadner, Gritta Janka, Stephan Ladisch, Milen Minkov, and Amir Shahlaee for their valuable comments on the manuscript.*

Submitted for publication Jul 24, 2009; last revision received Jan 11, 2010; accepted Mar 2, 2010.

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## Appendix

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